Caffeine in Parkinson disease

Better for cruise control than snooze patrol?

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Caffeine, the world's most widely used psychomotor stimulant, potentiates the antiparkinsonian effects of levodopa in preclinical models, as noted nearly 40 years ago.[1] The findings prompted early placebo-controlled crossover studies of caffeine as an adjunct to levodopa or a dopamine agonist in Parkinson disease (PD).[2,3] No motor effect of caffeine was demonstrated other than exacerbation of dyskinesia. However, these small studies assessed caffeine at high doses (~1,100 mg/day, the equivalent of ~8 cups of brewed coffee/day), at which most subjects reported restlessness and insomnia. By contrast, another small study reported that caffeine at a much lower dose of 100 mg/day helped improve freezing of gait, though tolerance to caffeine seemed to limit benefit.[4]

In this issue of *Neurology*®, Postuma et al.[5] report the results of a randomized controlled trial of caffeine as a treatment of excessive daytime sleepiness in PD. Although efficacy for improving wakefulness assessed under the primary outcome did not reach statistical significance (yielding Class I evidence against such an indication in PD), a secondary outcome analysis provided evidence in support of an antiparkinsonian motor effect of caffeine. Sixty-one subjects with PD with documented daytime sleepiness and moderate motor symptoms, treated with ~600 mg per day of levodopa on average, were randomized 1:1 to placebo vs 100 mg caffeine twice a day for 3 weeks before advancing to 200 mg twice daily for 3 more weeks. After 6 weeks, those in the caffeine group showed improvement relative to controls on a standard clinical scale of parkinsonian dysfunction (close to 5 points on the total Unified Parkinson's Disease Rating Scale [UPDRS]), including its objective motor component and subscores for bradykinesia and rigidity, with similar findings at 3 weeks on the lower dose.

Several limitations of the study, as discussed by the authors, include the exploratory nature of the motor findings given the primary hypothesis of a nonmotor benefit; the possibility of incomplete blinding; and the brevity of treatment, leaving open the question of tolerance to caffeine. Nevertheless, these findings are noteworthy, the first to suggest antiparkinsonian effects of caffeine in a randomized clinical trial.

This Class II evidence that motor function in PD can be improved by caffeine is bolstered by mechanistic and clinical advances identifying adenosine A_{2A} receptor antagonism as the molecular basis of caffeine's psychomotor stimulant properties, and as a promising antiparkinsonian strategy. The discovery by the early 1980s that caffeine likely acts through antagonism of adenosine receptors[6] coupled with caffeine's antiparkinsonian effects in animal models[1] accelerated research into the neurobiology and neurotherapeutic potential of adenosine receptor blockade. Enthusiasm for targeting adenosine A_{2A} receptors in particular as a candidate antiparkinsonian strategy grew after the colocalization of A_{2A} receptors with dopamine D_2 receptors in striatopallidal output neurons, where their opposing cellular influences account for antiparkinsonian actions of both A_{2A} antagonists and D_2 agonists.[6,7] Moreover, the relatively restricted expression of CNS A_{2A} receptors to and within the striatum[7] (figure, A) suggests a low liability for neuropsychiatric side effects of A_{2A} antagonists, in contrast to existing nondopaminergic antiparkinsonian agents targeting much more widespread CNS receptors. Neuroimaging and behavioral data confirmed that caffeine indeed blocks striatal A_{2A} receptors (figure, B),[8] which appear required for its motor stimulant properties (figure, C).[9]

Caffeine's candidacy as an antiparkinsonian agent is strengthened further by progress made with several more specific A_{2A} antagonists (including istradefylline, preladenant, and tozadenant). Positive results have prompted ongoing phase II and III clinical trials of their antiparkinsonian potential. Epidemiologic and laboratory evidence that caffeine and specific A_{2A} antagonists may offer additional benefits of slowing the underlying neurodegenerative process or

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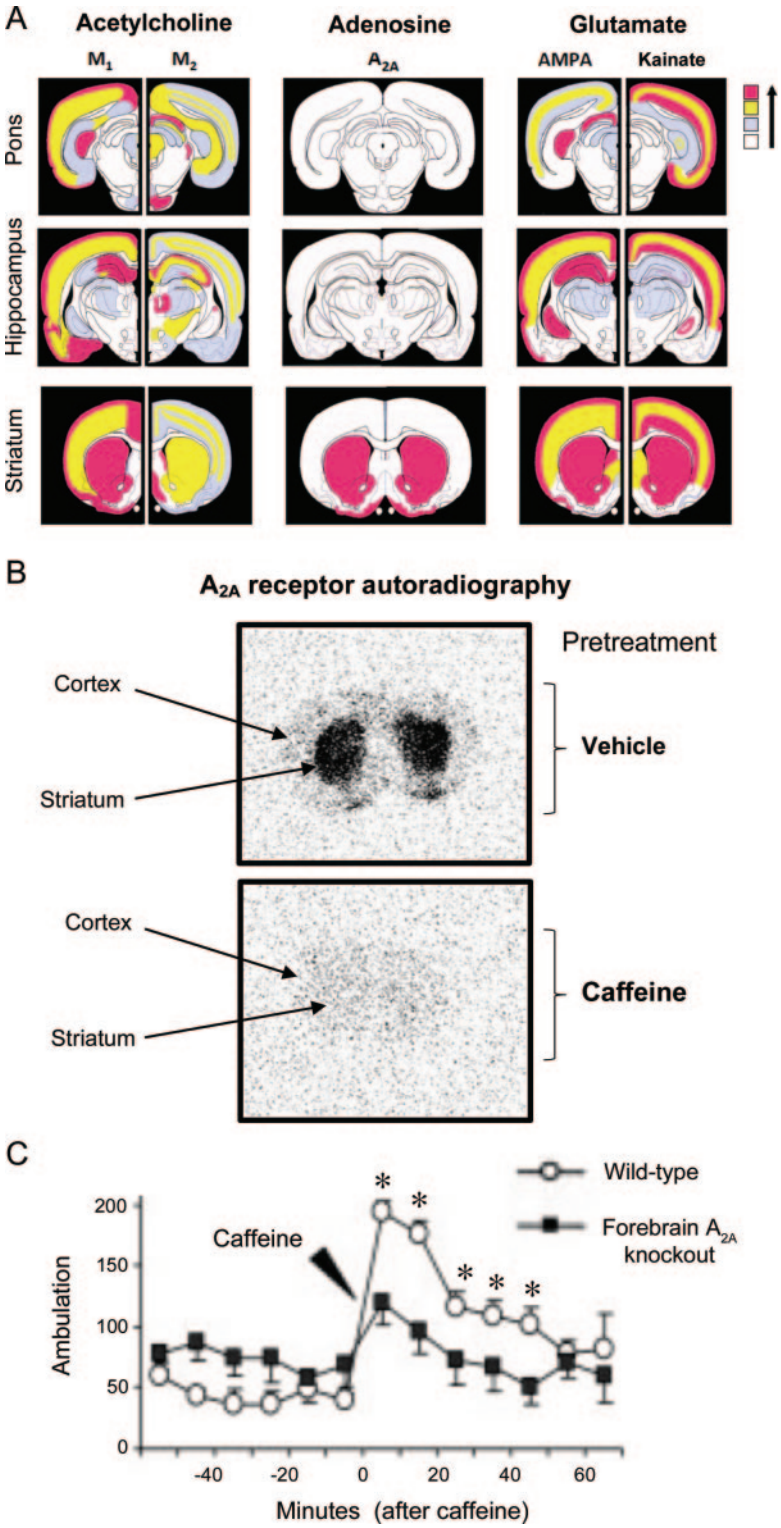
Figure Potential antiparkinsonian actions of caffeine through its blockade of adenosine A_{2A} receptors on striatal neurons



(A) Muscarinic acetylcholine receptors (left) and ionotropic glutamate receptors (right) are targeted by nondopaminergic antiparkinsonian drugs (e.g., trihexyphenidyl and amantadine, respectively). By contrast, the adenosine A_{2A} receptor (center) is discretely expressed in the CNS, primarily in the striatum.[7] (B) Caffeine blocks adenosine receptors including the A_{2A} receptor. A moderate dose of caffeine can markedly displace binding of endogenous adenosine or a radiolabeled A_{2A} receptor ligand.[8] (C) The psychomotor motor stimulant actions of caffeine require adenosine A_{2A} receptors, particularly those expressed on forebrain neurons as demonstrated by attenuated locomotor effects of caffeine in mice with a conditional knockout of neuronal A_{2A} receptors.[9] For details, see cited publications and references therein, from which panels are adapted with permission.

reducing the risk of dyskinesias,[7] while clinically untested, has helped justify a high level of investment in adenosine antagonism for PD.

Nevertheless, the findings of Postuma et al.[5] underscore the longstanding question of whether the greater selectivity for A_{2A} (over A_1 and other adenosine receptor subtypes) offered by adenosine antagonists in commercial development constitutes a clinically meaningful advantage over the relatively nonspecific adenosine antagonism of caffeine. Such benefits should be substantial to offset the unmatchable advantages of caffeine's long-term safety experience and cost. Moreover, as the authors note, their preliminary findings that caffeine improved total UPDRS score by 4–5 points, if substantiated, may be comparable to UPDRS improvements achieved to date with specific A_{2A} antagonists.

There are theoretical disadvantages of caffeine and its greater likelihood for "off-target " effects. For example, caffeine classically produces tolerance to its motor stimulant actions; by contrast, preclinical studies of a specific A_{2A} antagonist failed to demonstrate tolerance to motor stimulant and antiparkinsonian effects.[10] Ultimately, head-to-head comparisons may be required to distinguish the utility of A_{2A}-specific and mixed adenosine receptor antagonists for treating the motor symptoms or other features of PD. For the time being, the results of Postuma et al.[5] should encourage further investigation of a potential antiparkinsonian ("cruise control") benefit of caffeine without entirely discouraging pursuit of its putative alerting ("snooze patrol") action in PD. Although current data do not warrant a recommendation of caffeine as a therapeutic intervention in PD, they can reasonably be taken into consideration when discussing dietary caffeine use.

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